

Prokaryotic Sex: Eukaryote-like Qualities of Recombination in an Archaeal Lineage

Genetic exchange within one Archaeal lineage is a bit like sex in eukaryotes — cells fuse and huge segments of DNA are recombined — with consequences for the spread of adaptations across species.

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Two decades ago, Moshe Mevarech and colleagues discovered an extraordinary mode of recombination in an Archaeal taxon — cells of *Haloferax* can recombine through cell fusion [1]. After two cells fuse, their genomes can recombine, and then the fused cell can resolve into two cells, each with a single chromosome. The authors noted that fusion-based recombination holds some resemblance to mating in the eukaryotes.

As reported in this issue of *Current Biology*, Mevarech and colleagues [2] from Tel Aviv University and the University of Connecticut have recently investigated the population genetics of fusion-based recombination in *Haloferax*, and have challenged views on the evolutionary effects of genetic exchange in prokaryotes. Naor *et al.* [2] first challenged the widely accepted view that recombination in prokaryotes involves transfer of short DNA segments. In principle, cell fusion could enable recombination of enormous segments of DNA, possibly up to the 50:50 mix of genes seen in eukaryotic sex. Naor *et al.* found that ~17% of the genome is transferred in *Haloferax* fusion; at 475 kilobases, these segments are much larger than generally seen in bacterial recombination [3].

The huge size of recombined segments in *Haloferax* could negatively and positively impact the course of adaptive evolution. *Haloferax* loses one advantage seen in Bacteria for transferring short segments across populations. In Bacteria, transfers of short segments allow a recipient to acquire a niche-transcending adaptation (which is beneficial in different niches and genetic backgrounds, e.g., resistance to an antibiotic) without also acquiring niche-specifying genes from the donor

(which may be harmful to the recipient) [3]. We therefore hypothesize that in *Haloferax* and other cell-fusion systems, niche-transcending adaptations may not transfer as easily as in the Bacteria. On the other hand, the huge size of recombined segments may foster the transfer of extremely complex adaptations that could not otherwise be transferred [4], including possibly the ancient transfer of aerobic metabolism from Bacteria into Archaeal methanogens [5].

Naor *et al.* also challenged our understanding of barriers to genetic exchange between divergent species, finding surprisingly little sexual isolation between two *Haloferax* species (Figure 1). The 14% sequence divergence between these species would have predicted a 1,000-fold reduction in recombination rate in Bacteria [6], but recombination in this system was reduced by only a factor of about 40.

Why is *Haloferax* recombination so much less sensitive to sequence divergence? The authors noted that the borders of recombination frequently coincided at one end with chromosome locations of very high inter-species identity, including rRNA and tRNA genes. This is consistent with Bacterial recombination, which requires a nearly perfect match between donor and recipient sequences at one [7] or both [8] ends of the donor segment, while the sequence divergence between ends is of no consequence [9]. Thus, interspecies recombination in *Haloferax* was augmented by segments ending at the nearly identical tRNA and rRNA genes.

The enormous sizes of transferred segments in *Haloferax* may explain why recombination junctions so frequently occurred at regions of unusually high identity. We hypothesize an iterative process whereby the original two donor-segment ends are tested against the recipient genome; if they fail to

match, the ends may be cut to a random extent by exonucleases, and then the newly revealed ends are tested, and so on. This would increase the probability that eventually a reduced donor segment would sufficiently match a sequence from the recipient. We suggest this process would be particularly successful in organisms that recombine through cell fusion, as the donor segments start out exceptionally long. This hypothesis predicts that more-closely-related organisms may recombine after a smaller number of cuts; so more-distant crosses would yield shorter recombinant segments, a pattern observed in *Bacillus* transformation [3].

The authors suggest that horizontal genetic transfer would be particularly easy between species where cell fusion occurs. While recombination between already-fused cells seems almost unhindered by the sequence divergence between *Haloferax* species, it is possible that resistance to cell fusion may increase with greater phylogenetic distances. It will be interesting to find out the phylogenetic distance over which cells can readily fuse, and also how widespread cell fusion is over the Archaea. So far we know that *Haloferax* failed to recombine with two related genera through cell fusion [10] and that fusion-based recombination can occur in the distantly related Archaeal *Sulfolobus* [11].

Finally, the authors challenge the conclusion from bacterial studies that recombination is rare in prokaryotic systems. Their experiments in laboratory culture yielded recombination rates around 10^{-4} , which are high compared to other prokaryotic systems [12]. However, it is important to keep in mind that the rate of recombination in nature is not easily simulated in the laboratory. This is because recombination rates depend on the rate at which cells encounter one another (limited by densities and sharing of microhabitats), as well as the likelihood of cells being in a physiological state conducive to recombination, parameters that are generally unknown in nature.

In contrast, sequence analyses of organisms sampled from nature can yield a 'retrospective' recombination rate, averaged over time and habitats, while avoiding the biases of

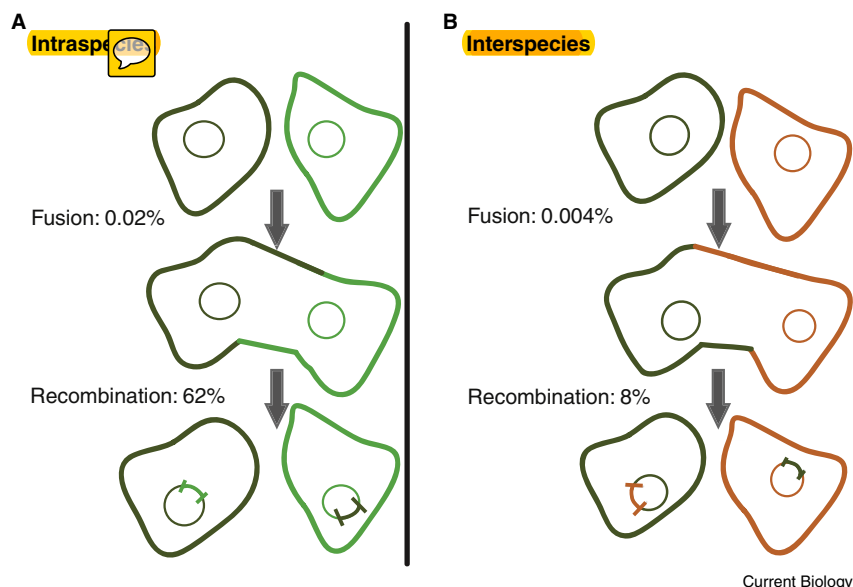


Figure 1. Cell fusion and recombination in *Haloferax*.

Genetic exchange can occur in *Haloferax* through cell fusion followed by recombination, within (A) and between (B) species. Both cell fusion and recombination are reduced between species (by 5-fold and 8-fold, respectively), yielding an overall 40-fold reduction in genetic exchange. This is much less sexual isolation than would be expected for bacterial species that are equally divergent (expected 1000-fold reduction). These results suggest that genetic transfer may be easier among archaean than among bacterial species. However, it is not yet known over what phylogenetic distances archaean cells can easily fuse.

experimental studies. Naor *et al.* [2] noted that while a retrospective phylogenetic analysis in the closely related *Halorubrum* did not indicate exceptionally high recombination rates in nature [12,13], frequent recombination was indicated by near-zero levels of linkage disequilibrium (i.e., little association of alleles across gene loci). However, analyses of linkage disequilibrium yield a less resolved estimate of recombination than phylogenetic analyses of sequence data, and others have found that a low rate of recombination near the mutation rate can yield near-zero linkage disequilibrium [12,14].

The authors also argue for a high recombination rate on the basis of an apparent failure of 'periodic selection' to eliminate diversity within two phylogenetic groups (phylotypes) in *Halorubrum* [13]. The idea is that if recombination rates are truly low, each adaptive mutation should bring about natural selection that 'sweeps' the diversity, genome-wide, within an ecologically homogeneous population (ecotype) [15]. The authors note that diversity within each phylotype was not purged genome-wide; instead, a single

sequence at one gene locus spread across an entire phylotype, while elsewhere on the chromosome the phylotype was much more diverse. They suggest this implies frequent recombination, as have others observing similar patterns [16–18]. However, periodic selection can purge diversity only within a single ecotype, and the observed single-gene sweeps have likely involved transfer of adaptive genes across different ecotypes and are therefore outside the predictions of periodic selection theory. Moreover, only a single transfer of an adaptive gene between ecotypes is sufficient to homogenize different ecotypes at the transferred gene, while the ecotypes remain divergent elsewhere in the genome [19,20]. We conclude that the evidence for rampant recombination in *Halorubrum* is not compelling.

In summary, the authors have revealed a portion of the prokaryotic world where huge segments of the genome can be transferred and organisms care little about their divergence from potential sexual partners. It will be interesting to find how common fusion-based dynamics are within the Archaea.

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